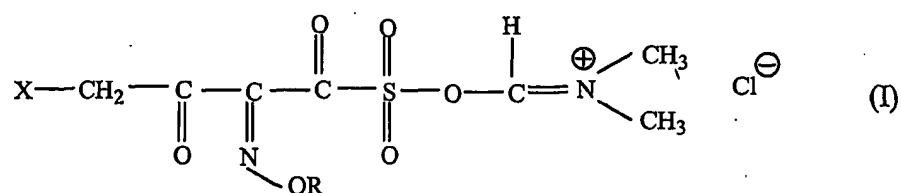


Claims :

1. A novel 4-halo-2-oxyimino-3-oxo butyric acid-N, N-dimethyl formiminium chloride chlorosulfate of formula (I) useful in the preparation of cephalosporin antibiotics



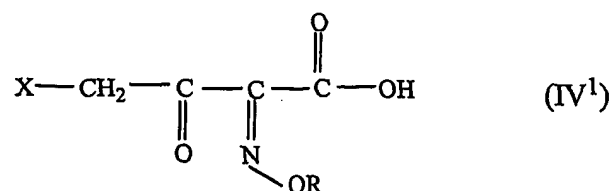
wherein

X is chlorine or bromine;

R is hydrogen, C₁₋₄ alkyl group, an easily removable hydroxyl protective group, -CH₂COOR₅, or -C(CH₃)₂COOR₅

wherein R₅ is hydrogen or an easily hydrolysable ester group.

2. A process for preparation of compound of formula (I) comprising reacting 4-halo-2-oxyimino-3-oxobutyric acid of formula (IV¹),



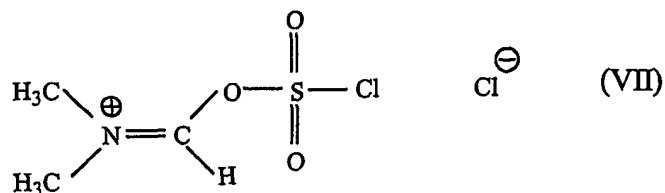
wherein

X is chlorine or bromine;

R is hydrogen, C₁₋₄ alkyl group, an easily removable hydroxyl protective group, -CH₂COOR₅, or -C(CH₃)₂COOR₅

wherein R₅ is hydrogen or an easily hydrolysable ester group.

with N, N-dimethylformiminium chloride chlorosulphate of formula (VII)

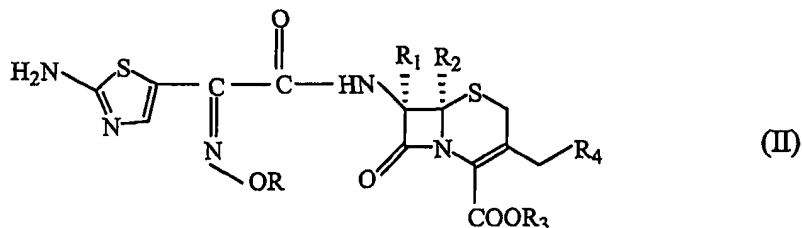


in an organic solvent at a temperature ranging from -30°C to -15°C .

3. A process according to Claim 2, wherein the organic solvent is selected from chlorinated solvents such as dichloromethane, dichloroethane, or chloroform; aromatic hydrocarbons such as benzene or toluene; and nitriles such as acetonitrile, propionitrile or butyronitrile.

4. A process according to Claim 2, wherein the molar ratio of compound of formula (VII) to compound of formula (IV¹) is between 1.1 to 1.3.

5. A process for preparation of a cephalosporin compound of formula (II),



wherein

R is hydrogen, C₁₋₄ alkyl group, an easily removable hydroxyl protective group, -CH₂COOR₅, or -C(CH₃)₂COOR₅

wherein R₅ is hydrogen or an easily hydrolysable ester group.

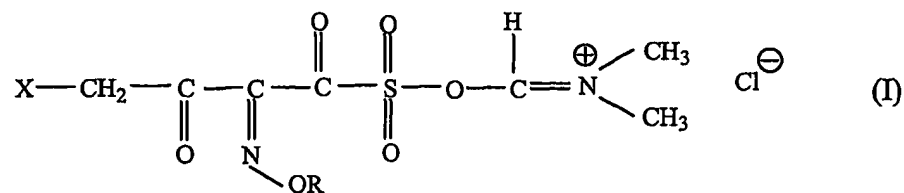
R₁ is hydrogen or -OCH₃;

R₂ is hydrogen;

R₃ is hydrogen, a negative charge or together with the COO⁻ group to which R₃ is attached is an ester, or an alkali or alkaline earth metal,

R₄ is hydrogen or is a substituent useful in cephalosporin chemistry;

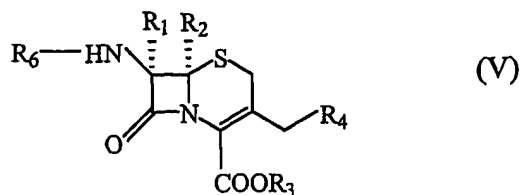
comprising reaction of compound of formula (I)



5 wherein X is chlorine or bromine; R is hydrogen, C₁₋₄ alkyl group, an easily removable hydroxyl protective group, -CH₂COOR₅, or -C(CH₃)₂COOR₅, wherein R₅ is hydrogen or an easily hydrolysable ester group

with 7-amino cephalosporanic acid of formula (V),

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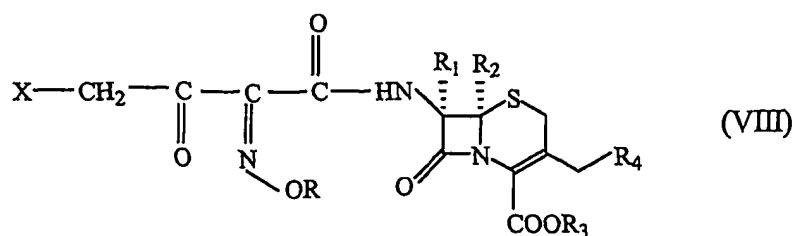


wherein R₁ is hydrogen or -OCH₃; R₂ is hydrogen; R₃ is hydrogen, a negative charge or together with the COO⁻ group to which R₃ is attached is an ester, or an alkali or alkaline earth metal, or is a silyl group; R₄ is hydrogen or is a substituent useful in cephalosporin chemistry; R₆ is hydrogen or a silyl group with the proviso that, when R₃ is hydrogen R₆ is also hydrogen; when R₃ is a silyl group R₆ is also a silyl group; and when R₃ is an ester, or an alkali or alkaline earth metal R₆ is hydrogen

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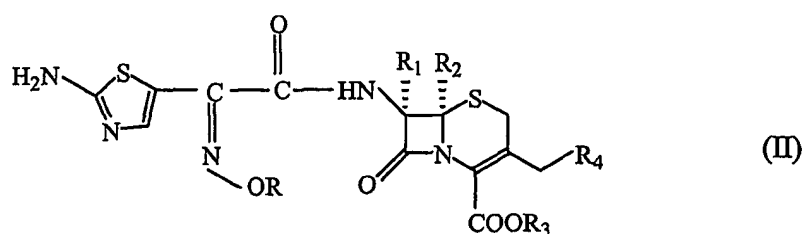
to give 7-[(4-halo-2-oxyimino-3-oxobutyramido-3-substituted-3-cephem-4-carboxylic acid of formula (VIII),



wherein X, R, R₁, R₂ and R₄ have the same meanings as defined hereinearlier, and R₃ is hydrogen, a negative charge or together with the COO⁻ group to which R₃ is attached is an ester, or an alkali or alkaline earth metal.

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followed by cyclisation of compound (VIII) with thiourea to give compound of formula (II),



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wherein R and R₅ are as defined above; R₁ is hydrogen or -OCH₃; R₂ is hydrogen; R₃ is hydrogen, a negative charge or together with the COO⁻ group to which R₃ is attached is an ester or an alkali or alkaline earth metal; R₄ is hydrogen or is a substituent useful in cephalosporin chemistry.

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6. A process according to Claim 5, wherein the reaction of compound (I) and compound (V) to give compound (VIII) is carried out in an organic solvent and in the presence of a base at a temperature ranging from -80⁰ C to -15⁰ C,.
- 20 7. A process according to Claims 5 or 6, wherein the organic solvent is selected from chlorinated solvents such as dichloromethane, dichloroethane, and chloroform; aromatic hydrocarbons such as benzene and toluene; nitrile solvents such as acetonitrile, propionitrile and butyronitrile; ethers such as tetrahydrofuran and dioxane.
- 25 8. A process according to Claims 5 or 6, wherein the base is selected from N, N dimethyl aniline, diethyl amine, and pyridine.

9. A process according to Claims 5 or 6, wherein the molar ratio of compound (I) to the cephalosporin compound (V) is between 1.1 to 2.0, preferably between 1.2 to 1.5.
10. A process according to Claims 5 or 6, wherein the preferred temperature is between –
5 55⁰ C to –25⁰ C.
11. A process according to Claim 5, wherein the reaction of compound (VIII) and thiourea to give the cephalosporin compounds of formula (II) is carried out in a mixture of organic solvent and water and in the presence of a base at low to ambient temperature.
- 10 12. A process according to Claims 5 or 11, wherein the the organic solvent is selected from chlorinated solvents such as dichloromethane, dichloroethane, and chloroform; aromatic hydrocarbons such as benzene and toluene; nitrile solvents such as acetonitrile, propionitrile and butyronitrile; ethers such as tetrahydrofuran and dioxane.
- 15 13. A process to Claims 5 or 11, wherein the base is selected from alkali metal carbonates, such as sodium carbonate, potassium carbonate and lithium carbonate; alkali metal hydrogen carbonates, such as sodium hydrogen carbonate and potassium carbonate; and alkali metal acetates, such as sodium acetate and potassium acetate.
- 20 14. A process according to Claims 5 or 11, wherein the temperature is between –5⁰ C to 40⁰ C, preferably between –10⁰ C to 30⁰ C.
- 25 15. A process according to Claim 5, wherein the compound of formula (II) is any one of
- 26 i) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid i.e. cefdinir,
- 30 ii) 7-[(Z)-2-(2-amino-4-thiazolyl)-2-methoxyimino)acetyl]amino-3-[(1Z)-2-(4-methyl-5-thiazolyl)ethenyl -3-cephem-4-carboxylic acid, i.e. cefditoren and the pivaloyloxymethyl ester i. e. cefditoren pivoxil,

- iii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1-methylpyrrolodino) methyl-3-cephem-4-carboxylate i.e. cefepime,
- iv) 7-[(Z)-2-(2-aminothiazol-4-yl)methoxyiminoacetamido]-3-methyl-3-cephem-4-carboxylic acid i.e. cefetamet, and the pivaloyloxymethyl ester i. e. cefetamet pivoxil,
- v) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-carboxymethoxyiminoacetamido]-3-vinyl-3-cephem-4-carboxylic acid i.e. cefixime,
- vi) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[1-methyl-1H-tetrazol-5-yl]thio]methyl]-3-cephem-4-carboxylic acid i.e. cefmenoxime,
- vii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[[5-carboxymethyl]-4-methyl-2-thiazolyl]thio]methyl]- 3-cephem-4-carboxylic acid i.e. cefodizime,
- viii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[2,3-dihydro-2-(2-hydroxyethyl)-3-imino-1H-pyrazol-1-yl]methyl]- 3-cephem-4-carboxylic acid i. e. cefoselis,
- ix) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]cephalosporanic acid i.e. cefotaxime,
- x) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[92,3-cyclopenteno-1-pyridinium)methyl]- 3-cephem-4-carboxylic acid i.e. cefpirome,
- xi) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methoxymethyl-3-cephem-4-carboxylate- i.e. cefpodoxime and the 1-methylethoxycarbonyloxy ether i. e. cefpodoxime proxetil,

- xii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl-5,6,7-tetrahydroquinolinium-4-carboxylic acid inner salt i. e. cefquinome,
- 5 xiii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methylethyl)oximinoacetamido]-3-[pyridinium]methyl-3-cephem-4-carboxylic acid inner salt i. e. ceftazidime,
- 10 xiv) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[2-(5-methyl-1,2,3,4-tetrazoyl)-methyl-3-cephem-4-carboxylic acid i. e. cefteram and the and the pivaloyloxymethyl ester i. e. cefteram pivoxil,
- 15 xv) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(2-furanylcarbonyl)thio]methyl]-3-cephem-4-carboxylic acid i. e. ceftiofur,
- xvi) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-cephem-4-carboxylic acid i. e. ceftizoxime,
- 20 xvii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[[2,5-dihydro-6-hydroxy-2-methyl-5-oxo-as-triazin-3-yl)thio]methyl]-3-cephem-4-carboxylic acid i. e. ceftriaxone, and
- 25 xviii) 7-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(1,2,3-thiadiazol-5-ylthio)methyl]-3-cephem-4-carboxylic acid i. e. cefuzonam.